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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,431	MILTON ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *1-21,31-59 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 8/11/04, claims 22, 24 and 28 have been amended. Claims 1-21 and 31-59 and 62 remain withdrawn from consideration. Claims 22-30, 60, 61 are examined in this Office action.

Applicants' arguments filed 8/11/04 have been considered and found not persuasive.

✧

Claims 29-30 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The cited claims recite the term "about" in reference to a range, thus rendering the claims indefinite as to the upper and lower limits. It is suggested that the term "about" be deleted.

✧

The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Andya (USP 6,267,958).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Andya discloses a freeze-dried formulation that comprises a therapeutic peptide, a micelle-forming surfactant, and a bulking agent. Relevant passages include those at col 15, line 36+, col 15, line 61+ and col 6, line 45+. The formulations are asserted (e.g., col 1, line 63+) to be stable. Also asserted is that a high protein concentration can be obtained by reconstituting the lyophilized compositions, yielding a reconstituted formulation that is also stable (col 1, line 66+). In addition, there are numerous references to mannitol.

In response to the foregoing, applicants have begun by arguing that a §102 rejection over Andya (taken by itself) would be improper. While this may be true, it is a moot

point. Next, applicants have argued that Andya "teaches away" from the claimed invention. In support of this assertion, applicants point to the fact that Andya suggests using proteins which have a MW of at least 15 kD. However, this does not, in any way, amount to a "teaching away" from the claimed invention. First, some of the peptides listed (col 6, line 45+) have molecular weights substantially less than 15 kD. For example, calcitonin (col 6, line 5) consists of 32 amino acids and has a molecular weight of 3600 g/mol. But even if it were true that all of the peptides listed had a molecular weight in excess of 15 kD, this would not amount to a "teaching away" from the claimed invention. Andya asserts that the lyophilized formulations of his invention are stable, and permit one to produce "reconstituted formulations" (e.g., col 1, line 66+) in which the protein concentration is significantly higher than that of the pre-lyophilized formulation. Thus, for the peptide chemist (of ordinary skill) endeavoring to produce a lyophilized peptide formulation to be used as such, or to be reconstituted, he would have motivation to use the techniques described in Andya. In order for there to be a "teaching away" there would have to be a teaching that if the invention is practiced on a given genus of peptides of which echinocandins are a member, that somehow "failure" will result. However, there is no evidence of such failure, and there is no suggestion of such failure in Andya. In fact, there isn't even suggestion of such failure by applicants. Certainly, there is no question that water can be removed from a

mixture containing an echinocandin and water. In addition, there is no evidence that decomposition would occur if an echinocandin were combined with the non-peptide constituents of Andya, and the resulting mixture lyophilized. Nor have applicants even offered speculation as to why one might expect some sort of decomposition to occur. An infectious disease specialist endeavoring to treat fungal infections would have been motivated to use an echinocandin. By using the formulations of Andya, the infectious disease specialist (of ordinary skill) would have expected to produce lyophilized formulations that would be stable on storage, and would permit the production of a concentrated peptide solution at a later time.

There is no evidence, or even suggestion in any of the references, or even in applicants' own arguments as to what sort of "failure" might occur, or why it would occur. The practitioner of the Andya invention would have had no reason to expect anything but success if he prepared lyophilized formulations of echinocandins.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5,541,160) or Abbot (USP 4,304,716) in view of Horikoshi (USP 4,348,384).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Horikoshi discloses freeze dried liposomes that contain therapeutic proteins. Horikoshi is primarily concerned with blood coagulation proteins. The reference discloses that the formulations offer various advantages such as reduced susceptibility to decomposition in the GI tract. Mannitol is disclosed at col 2, line 27. Horikoshi does not suggest using the freeze dried formulation to administer an echinocandin.

In response to the foregoing, applicants have argued that the drug formulation specialist of ordinary skill would not have been motivated to combine an echinocandin with the secondary ingredients (e.g., lecithin) disclosed in Horikoshi, because Horikoshi is concerned with preparing oral formulations of peptides, whereas (it is argued) the instant claims mandate i.v. or s.c. administration. However, applicants are not correct about what the claims require. Nowhere in the claims is there any suggestion as to the route of administration. Indeed, there is no suggestion (in the claims) of administration at all. The requirements of the claims would be met by the artisan (of ordinary skill) who did nothing more than to place the lyophilized formultion in a vial and left it there indefinitely. Beginning with this invalid premise (that the claims require oral administration), applicants have then gone on to argue that because echinocandins are of low water solubility, they would be difficult to formulate for oral

delivery. Applicants have provided no evidence of such difficulty, however. Furthermore, the practitioner of the Horikoshi invention would be incorporating the echinocandin into phospholipid micelles, in which case the amphiphilic nature of the echinocandin would present no hurdle, at least insofar as preparing the initial (pre-lyophilized) formulation is concerned. Applicants have also argued, beginning with the invalid premise (that the claims require oral administration), that the drug formulation specialist of ordinary skill would not have been motivated to use the Horikoshi formulations for i.v., or s.c. administration. Again, whatever the merits of this argument, the issue is moot. There is no requirement or suggestion in the claims that the formulation has to be administered parenterally. Perhaps if the claim were drawn to a method of administering a formulation intravenously or subcutaneously, there would be an issue for debate. But the point is moot, given the claims as rendered.

Next, applicants have argued (page 19, response) that the claimed formulations exhibit "enhanced stability". In support of this assertion, applicants have pointed to page 29 of the specification (tables 3 and 4). The first point about this data is that it is not entirely clear what was done. One interpretation is that table 3 represents stability in aqueous solution, whereas table 4 represents lyophilized mixtures. Assuming that this is true, the next point is that there are very few direct comparisons between the two tables. In most cases, the secondary ingredients are different in the two cases.

Further, if one looks at the first three entries of the two tables, one finds that the freeze dried formulation (table 4) is actually less stable than the aqueous solution (table 3). Thus, the data does not actually support the proposition that the lyophilized formulation is any better than the aqueous formulation. But suppose that, at some point in the future, applicants are able to demonstrate that the rate of decomposition of an aqueous formulation at 40 °C is greater than that of a lyophilized formulation (at the same temperature). The first question will be that of the nature of the decomposition products. If all of the decomposition is due to "inactive" ingredients (e.g., polysorbate and PEG), this will not work in applicants favor in arguing for unexpected results. But suppose that, at some point in the future, applicants are able to demonstrate that the rate of decomposition of an aqueous formulation at 40 °C is greater than that of a lyophilized formulation and that the rate of decomposition of the echinocandin is greater in the aqueous solution than in the lyophilized preparation. Even then the results would not be effective to overcome this rejection. The reason is that the comparison of aqueous versus lyophilized has no direct bearing on any of the §103 rejections. The secondary reference in this case (Horikoshi), and in all other cases has already provided the teaching for, and the motivation for lyophilization. The fact that an aqueous solution might be better or worse than the corresponding lyophilized formulation does not amount to an "unexpected result". For a given experimental

observation to qualify as an "unexpected result", it must directly address the difference between what is claimed, and what is explicitly taught. Whatever deficiencies there might be in this ground of rejection (and none is conceded), the failure to teach lyophilization is not among them.

Applicants data, even apart from its experimental defects, does not even provide the pretense of "unexpected results". The data largely constitutes an "apples and oranges" comparison with regard to what the reference teach and do not teach. By way of contrast, consider the following hypothetical claim:

> *100. A method of enhancing the stability of a lyophilized echinocandin-containing formulation comprising the step of incorporating a micelle-forming surfactant, and a bulking agent into said formulation prior to lyophilization.*

And suppose further that applicants had shown that the rate of decomposition of lyophilized echinocandin was dramatically reduced when in the presence of a "micelle-forming surfactant" and a "bulking agent" as compared to the absence of these two components. Such a result, in conjunction with the indicated claim, would at least begin to address the issue of the "differences" between the prior art and the claim (i.e., claim "100"). But the situation at hand is far removed from this. The claims are drawn to compositions *per se*, not to any method of making or using them. And the data of tables 3 and 4 (instant specification) does not address the "differences" between the prior art and the claimed invention. And finally, one could easily conclude that whatever

benefits might accrue to the claimed compositions are due primarily to the presence of polysorbate 80, a compound which is not required or suggested by most of the claims.

Next, applicants have pointed to Boulomie (USP 6,284,277), and have argued that this patent asserts that the factors giving rise to stable lyophilized formulations is unpredictable. However, in the passage at col 4, lines 5-28, the term "unpredictable" is not used. What is stated is the following:

> "...[The prior art] does not make it possible to obtain ...information on the subject of the relationships between the structure of a freeze-dried product and its stability".

Perhaps it is true that there exist agents which destabilize lyophilized peptide formuations. If so, none has been identified. But the more important point is that Boulomie provides no evidence or suggestion that the lyophilized formulations of Horikoshi will be anything but stable. Horikoshi asserts that his formulations are stable, Boulomie does not assert that the formulations of Horikoshi are <u>not</u> stable. Accordingly, no reason has been provided as to why the drug formulation specialist of ordinary skill would have expected the formulations of Horikoshi to be unstable, whether they contain an echinocandin or factor VIII.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543)

or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Staniforth (USP 6,153,224).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Staniforth discloses dry powder formulations containing pharmaceutically active compounds such as peptides and proteins (col 7, line 44-56). There are several references to lecithin and phosphatidylcholine (e.g., col 5, line 43), which meet the requirement for a "micelle-forming surfactant". Staniforth does not disclose echinocandins. Staniforth also does not use the term "freeze dried" or "lyophilized" to describe his formulations. However, the issue here is whether or not there is a physical difference that would arise if one were to take a formulation of Staniforth, add water, and then lyophilize the resulting aqueous mixture. In reality, there is no reason to expect any substantive change in the composition (as a consequence of hydration/dehydration). It is also noted also that Staniforth suggests a milling procedure to reduce particle size. However, (a) the claimed formulations do not preclude a milling procedure, and (b) Staniforth does not require a milling procedure. Thus, the fact that such a milling procedure may be mentioned in the reference, but not explicitly mandated by the instant claims, does not impart novelty to the claimed invention.

The principal basis of applicants' traversal is to apply an invalid premise, i.e., that the claims mandate i.v. or s.c. administration. However, since the premise is invalid, all

arguments flowing therefrom are irrelevant. In the event that applicants decide to claim a method of iv or sc administration, these arguments might become appropriate.

Applicants have also argued that the instant formulations can form a "cake", and the Staniforth formulations cannot. Whether this is true or not, the point is moot. There is no suggestion in any of the claims that a cake can be, or should be formed.

Applicants have also argued that Boulhoumie has asserted that preparation of stable lyophilized preparations is unpredictable. However, Boulhoumie did not use the term "unpredictable". Further, Boulhoumie has not asserted that the Staniforth compositions are unstable. At the same time, Staniforth recognizes (col 1, line 42+) the importance of chemical and physical stability. The fact that there may exist an unstable formulation somewhere does not mean that the Staniforth formulations are unstable.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Tarara (USP 6565885)

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Tarara discloses pharmaceutical

compositions which can contain (col 13, line 58) bioactive peptides. Freeze drying is disclosed at col 22, line 1. Incorporation of phosphatidylcholines is disclosed e.g., at col 10, line 31+, and the use of surfactants such as sorbitan trioleate is disclosed at col 10, line 59. Mannitol is disclosed at col 12, line 35. Tarara does not suggest using the freeze dried formulation to administer an echinocandin.

In response to the foregoing, applicants have argued that Tarara fails to teach lyophilization. However, this is not correct. Lyophilization is discussed at col 22, line 1+. The argument could stop here and be sufficient. But even if Tarara had not disclosed lyophilization, the rejection would still be justified. As it happens, the claims are not drawn to a method of lyophilizing a mixture. The claims are drawn to compositions *per se*. The claims encompass any composition that could have been made by lyophilization, even if it was not made that way. To take an extreme example, suppose that someone obtained a handful of sand from a beach, and subsequently divided the handful of sand into two equal parts. The "first" half is placed in a jar. To the "second" half is added water, and the water is subsequently removed at very low pressure. If applicants were presented with the two samples of sand, by what physical or chemical test would applicants determine which had been lyophilized and which had not? Again, the claims are not drawn to a method of lyophilizing something; the claims encompass any composition that could have been

made by lyophilization, even if it was not made that way. Even if the reference had mandated that the compositions be spray dried, the compositions would still be equivalent to compositions which had been lyophilized.

Next, applicants have argued that the specification discloses, on page 2 (lines 1-15) that echinocandin readily undergoes thermal degradation. However, this is not disclosed within the cited passage. The examiner will stipulate that if one heats a solution of an echinocandin at a temperature of 40 °C for a month, that some decomposition can be detected. However, the fact that this may be true is irrelevant to the discussion. The spray drying process subjects the solution of peptide to an elevated temperature for a time period of perhaps a few seconds. There is no evidence that subjecting a solution of an echinocandin at a temperature of, e.g., 75 °C for 5 seconds will cause significant decomposition. But even suppose that the spray drying process cause 5% of the echinocandin to be converted to another compound. As it happens, the claims are drawn to compositions which comprise an echinocandin. If the composition contains a 95:5 mixture of an echinocandin and another peptide, that composition would still be encompassed within the scope of the claims. The instant claims exclude nothing.

Applicants have also argued that Boulhoumie has asserted that preparation of stable lyophilized preparations is unpredictable. However, Boulhoumie did not use the term "unpredictable". Further, Boulhoumie has not asserted that the Tarara compositions are

unstable.

Thus, (a) the reference discloses lyophilization, which applicants have not acknowledged, (b) even if lyophilization had not been discussed, the reality is that there is overlap between the physical properties of a lyophilized peptide mixture, and a spray-dried peptide mixture, (c) there is no evidence that spray drying would cause degradation of an echinocandin, (d) even if some decomposition occurred during spray drying, the claims do not exclude formulations which contain peptidic impurities, and (e) there is no evidence that the compositions of Tarara are unstable.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. 103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Backstrom (USP 5,952,008).

As indicated previously, each of the primary references discloses echinocandins. Backstrom discloses peptide-containing compositions that can be obtained (col 8, line 60) by freeze-drying.

In response, applicants have argued that the instant claims mandate i.v. or s.c. administration. However, this is not the case. There is nothing in the claims that

would preclude pulmonary administration. There is also nothing in the claims that would preclude one from placing the composition in a vial and merely using the vial as a paperweight. Thus, it may be true that Backstrom is teaching "away" from iv and sc administration, but at the same time, Backstrom is teaching "towards" one embodiment of the claimed invention.

Next, applicants have argued that of the surfactants disclosed by Backstrom, none will form micelles. However, this is not correct. For example, the following agents will form micelles: sodium caprate (col 3, line 2); phosphatidylcholine (col 6, line 5), octylglucopyranoside (col 6, line 17). Note that the claims do not actually require that micelles be formed, only that the compound in question possess the property of forming micelles under appropriate conditions.

Applicants have also argued that Boulhoumie has asserted that preparation of stable lyophilized preparations is unpredictable. However, Boulhoumie did not use the term "unpredictable". Further, Boulhoumie has not asserted that the Backstrom compositions are unstable.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543)

or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Bernstein (USP 6,689,390).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Bernstein discloses pharmaceutical compositions which can contain (col 6, line 65) bioactive peptides. Freeze drying is disclosed at col 9, lines 39-41. Incorporation of phosphatidylcholines is disclosed e.g col 2, line 41+. Mannitol is disclosed at col 10, line 7, and col 10, line 18.

In response, applicants have argued that Bernstein discloses microparticles, whereas the instant claims are drawn to microemulsions. Of all the assertions made by applicants, this one is the most untenable. The claimed compositions are the very antithesis of microemulsions. There is no suggestion of any kind that the claimed compositions might encompass microemulsions; moreover, both the claims and the specification "teach away" from microemulsions, at least for cases in which lyophilization is mandated. It may be true that Bernstein discloses microparticles, but it is also true that the reference discloses (col 9, lines 39-41) freeze drying. If one "freeze dries" microparticles, the result may be a composition that comprises microparticles, but that does not detract from the fact that the composition thus obtained has been freeze dried. If a composition has been freeze dried, it is a freeze dried composition and hence meets one of the critical limitations of the claims. The fact that applicants might not have considered the possibility of freeze

dried microparticles does not mean that freeze dried microparticles fail to meet the limitation of a freeze-dried physical entity.

Next, applicants have argued that because the reference refers to the non-bioactive agents as "excipients", that somehow the drug formulation specialist would believe that they should be eliminated from the mixture. However, there is nothing in the reference to suggest that excipients should be eliminated. The fact that the "non-bioactive agents" may serve a different role than has been asserted in the instant application does not detract from the fact that they are disclosed, and the artisan of ordinary skill would have had motivation to use them.

Next, applicants have argued that there is no suggestion in the reference to incorporate a compound in the mixture which has the property of forming micelles. However, this is not correct. For example, bile salts (col 9, line 16) are disclosed, as are phosphatidylcholines (col 2, line 41+). The claims do not actually require that micelles be formed, only that the compound in question possess the property of forming micelles under appropriate conditions.

The rejection is maintained.

✧

Claims 22-30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543)

or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Bouloumie (USP 6,284,277).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Bouloumie discloses freeze-dried pharmaceutical compositions. The presence of a bioactive protein is disclosed (e.g., col 19, line 47). In addition, there are several references to polysorbate 80 (e.g., col 19, line 11; col 19, line 29). The reference is also replete with references to mannitol. Bouloumie does not suggest using the freeze dried formulation to administer an echinocandin.

In response, applicants have argued that Bouloumie requires the presence of alanine, whereas (it is argued) the instant claims do not require alanine. It may be true that Bouloumie requires the presence of alanine, and that the instant claims do not require alanine. But it is also true that the instant claims encompass compositions in which alanine is present. The term "comprising" is open-ended language; when this term is used in reference to a composition (or a "formulation") it means that any compound can be present in addition to those recited. Thus, there is absolutely nothing in the language of claim 22, or in any of the other elected claims, which would exclude alanine.

Accordingly, the rejection is maintained.

✧

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Weers (USP 6,309,623).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Weers discloses pharmaceutical compositions. These may be obtained (col 25, line 63+) by a freeze-drying process. The use of phosphatidylcholine is suggested, e.g., at col 16, line 53+. Mannitol is disclosed at col 18, line 36.

In response, applicants have argued that compositions containing echinocandins are difficult to formulate due to instability. However, applicants have presented no evidence that this is the case. Next, applicants argue that Bouloumie asserts that one cannot predict which ingredients will result in stable lyophilized formulations. However, Bouloumie does not assert or even imply that all attempts at preparing lyophilized preparations will result in "failure". Nor does Bouloumie provide even one criterion for the expectation of failure. More importantly, Bouloumie does not assert or imply that the formulation of Weers will result in any kind of failure; at the same time, Weers asserts that all of the properties of his formulation are desirable, none are undesirable, and that all vestiges of "failure" are absent. Bouloumie provides no evidence or reasoning which

would suggest that if one were to incorporate an echinocandin into the Weers formulation, that any sort of instability or "failure" would result. Thus, given the assertion of stability by Weers, and the absence of any assertion by Bouloumie as the stability of the Weers formulation, there is no reason to expect anything but stability with respect to the Weers formulations.

Next, applicants argue that the instant claims are drawn to a cake. However, even a cursory examination of the claims reveals that this is entirely untrue.

Next, applicants argue that lecithin will not exhibit surfactant properties when present in the disclosed formulation. This might be true, but if so, that is not the end of the analysis. The instant claims impose no requirements on the circumstances under which the surfactant in question can form micelles. Moreover, a compound and its properties are inseparable. The properties of a compound when in the hands of one chemist will invariably be the same when in the hands of another chemist. Phosphatidylcholine is one of the best known micelle forming surfactants among those that are naturally occurring. If applicants are not aware that phosphatidylcholine readily forms micelles, references can be provided which show this to be the case. Of course, this does not mean that micelles will always and inevitably form regardless of circumstances. But the claims do not require such; the claims do not specify such. Similarly, polysorbate 80 will not form micelles under any and all conditions. Within the composition of (instant) claim 22, for

example, polysorbate 80 will not form micelles; the claim is drawn to an anhydrous formulation. But the fact that claim 22 is drawn to a formulation which does not contain micelles does not mean that polysorbate 80 does not possess the property of forming micelles under appropriate circumstances.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Staniforth (USP 6,475,523).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Staniforth discloses dry powder formulations containing pharmaceutically active compounds such as peptides and proteins (col 6, line 27). There are several references to lecithin (e.g., col 11, line 4; col 11, line 25), which meet the requirement for a "micelle-forming surfactant".

In response, applicants have argued that the claims are drawn to a method of administering formulations by iv or sc routes. However, this is not the case. The claims are drawn to compositions, and there is no suggestion or requirement that they be administered intravenously, intracerebralventricularly, or even that they be administered at

all. The claims encompass the possibility that the formulation is prepared, stored in a vial and never used. Further, the claims do not preclude the possibility that the formulations are inhaled for the purpose of treating a pulmonary infection. Next, applicants have argued that Boulhoumie has asserted that preparation of stable lyophilized preparations is unpredictable. However, Boulhoumie did not use the term "unpredictable". Further, Boulhoumie has not asserted that the Staniforth compositions are unstable. At the same time, Staniforth provides no indication that his compositions are unstable. Applicants have also argued that Staniforth does not disclose micelle-forming surfactants. However, lecithin is disclosed at various locations including the following: col 11, line 4; col 11, line 25. Applicants have also argued that Staniforth does not disclose a bulking agent. However, the desirability of using lactose is disclosed, e.g., at col 14, line 8+.

The rejection is maintained.

Claims 22-27, 29, 30, 60, 61 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Dellamary (USP 6,433,040).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen,

Balkovec, Abbot) discloses echinocandins. Dellamary discloses pharmaceutical compositions which can contain (col 18, line 58) bioactive peptides. Freeze drying is disclosed at col 25, line 44+. Incorporation of phosphatidylcholines is disclosed e.g., at col 16, line 45+, and the use of surfactants such as sorbitan trioleate is disclosed at col 16, line 62. Mannitol is disclosed at col 18, line 25.

In response to the foregoing, applicants have argued that the instant claims require, or at least suggest, that i.v. or s.c. administration is mandated. However, the claims require neither. Applicants have also argued that the instant claims require, or at least suggest, that the claimed composition is in the form of a cake. Again, the claims do not require this. Applicants have also argued that the reference does not disclose micelle-forming surfactants. However, incorporation of phosphatidylcholines is disclosed e.g., at col 16, line 45+, and the use of surfactants such as sorbitan trioleate is disclosed at col 16, line 62. Applicants have also argued that the claims specifically exclude block copolymers. While noting the passage on page 7, line 9+ of the specification, the reality is that the claims, as currently rendered, do not exclude block copolymers. If there is a particular entity that applicants would like to exclude from the claims, applicants may proceed as deemed appropriate. Until that time, however, the claims will be interpreted in accordance with patent law; as such, nothing is excluded from the claimed compositions.

The rejection is maintained.

✧

Claims 22-27, 29, 30, 60 are rejected under 35 U.S.C. §103 as being unpatentable over Debono (USP 4293489) or Burkhardt (USP 5,965,525) or Burkhardt (USP 5,932,543) or Chen (USP 5,198,421) or Balkovec (USP 5541160) or Abbot (USP 4,304,716) in view of Edwards (USP 5,985,309).

As indicated previously, each of the primary references (Debono, Burkhardt, Chen, Balkovec, Abbot) discloses echinocandins. Edwards discloses pharmaceutical compositions which can contain (col 12, line 1) bioactive peptides. Freeze drying is disclosed at various locations including col 8, line 48; col 14, line 5, and col 16, line 23. Incorporation of phosphatidylcholines is disclosed e.g., at col 7, line 15, and the use of surfactants such as sorbitan trioleate is disclosed at col 7, line 60.

In response to the foregoing, applicants have argued that the instant claims require, or at least suggest, that i.v. or s.c. administration is mandated. However, the claims require neither. Applicants have also argued that the instant claims require, or at least suggest, that the claimed composition is in the form of a cake. Again, the claims do not require this. Applicants have also argued that the reference does not disclose micelle-forming surfactants. However, incorporation of phosphatidylcholines is disclosed e.g., at col 7, line 15, and the use of surfactants such as sorbitan trioleate is disclosed at col 7, line

60.

The rejection is maintained.

✧

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600